```
=>  chemistry bioscience
CHEMISTRY IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> file chemistry bioscience
FILE 'ENCOMPLIT' ACCESS NOT AUTHORIZED
FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                        ENTRY    SESSION
FULL ESTIMATED COST                                      0.21       0.21

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FILE 'CORROSION' ENTERED AT 11:30:49 ON 15 APR 2004

FILE 'DISSABS' ENTERED AT 11:30:49 ON 15 APR 2004

FILE 'ENCOMPLIT2' ENTERED AT 11:30:49 ON 15 APR 2004

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FILE 'KOSMET' ENTERED AT 11:30:49 ON 15 APR 2004

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FILE 'RDISCLOSURE' ENTERED AT 11:30:49 ON 15 APR 2004

FILE 'RUSSCI' ENTERED AT 11:30:49 ON 15 APR 2004

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FILE 'TULSA2' ENTERED AT 11:30:49 ON 15 APR 2004

FILE 'USAN' ENTERED AT 11:30:49 ON 15 APR 2004

FILE 'WELDASEARCH' ENTERED AT 11:30:49 ON 15 APR 2004

FILE 'WSCA' ENTERED AT 11:30:49 ON 15 APR 2004

FILE 'ADISCTI' ENTERED AT 11:30:49 ON 15 APR 2004

FILE 'ADISINSIGHT' ENTERED AT 11:30:49 ON 15 APR 2004

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FILE 'BIOSIS' ENTERED AT 11:30:49 ON 15 APR 2004

FILE 'BIOTECHABS' ACCESS NOT AUTHORIZED

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FILE 'OCEAN' ENTERED AT 11:30:49 ON 15 APR 2004

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FILE 'PHAR' ENTERED AT 11:30:49 ON 15 APR 2004

FILE 'PHARMAML' ENTERED AT 11:30:49 ON 15 APR 2004

FILE 'PHIC' ENTERED AT 11:30:49 ON 15 APR 2004

FILE 'PHIN' ENTERED AT 11:30:49 ON 15 APR 2004

FILE 'SYNTHLINE' ENTERED AT 11:30:49 ON 15 APR 2004

FILE 'TOXCENTER' ENTERED AT 11:30:49 ON 15 APR 2004

FILE 'USPATFULL' ENTERED AT 11:30:49 ON 15 APR 2004

FILE 'USPAT2' ENTERED AT 11:30:49 ON 15 APR 2004

FILE 'VETB' ENTERED AT 11:30:49 ON 15 APR 2004

FILE 'VETU' ENTERED AT 11:30:49 ON 15 APR 2004

FILE 'WPIDS' ENTERED AT 11:30:49 ON 15 APR 2004

FILE 'WPINDEX' ACCESS NOT AUTHORIZED

=> s oulat/ same (oocyte (w) maturat/) (phosphodiesterase or PDE? or PDE4) and cAMP
OR IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s ovulat? (s) (oocyte (w) maturat?) (s) (phosphodiesterase or PDE? or PDE4) and cAMP
L1 0 FILE AGRICOLA
L2 0 FILE ALUMINIUM
L3 0 FILE ANABSTR
L4 0 FILE APOLLIT
L5 0 FILE AQUIRE
L6 0 FILE BABS
L7 0 FILE BIOCOMMERCE
L8 7 FILE BIOTECHNO
L9 5 FILE CABA
L10 0 FILE CAOLD
L11 2 FILE CAPLUS
L12 0 FILE CBNB
L13 0 FILE CEABA-VTB
L14 0 FILE CEN

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L15             0 FILE CERAB
L16             0 FILE CIN
L17             0 FILE COMPENDEX
L18             0 FILE CONFSCI
L19             0 FILE COPPERLIT
L20             0 FILE CORROSION
L21             0 FILE DISSABS
L22             0 FILE ENCOMPLIT2
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'OVULAT? (S) '
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'MATURAT?) (S) '
L23             0 FILE FEDRIP
L24             0 FILE GENBANK
L25             0 FILE INSPEC
L26             0 FILE INSPHYS
L27             0 FILE INVESTEXT
L28             0 FILE IPA
L29             0 FILE JICST-EPLUS
L30             0 FILE KOSMET
L31             0 FILE METADEX
L32             0 FILE NAPRALERT
L33             0 FILE NIOSHTIC
L34             0 FILE NTIS
L35             0 FILE PAPERCHEM2
L36             0 FILE PASCAL
L37             0 FILE PROMT
L38             0 FILE RAPRA
L39             0 FILE RDISCLOSURE
L40             0 FILE RUSSCI
L41             5 FILE SCISEARCH
L42             0 FILE STANDARDS
L43             0 FILE TULSA
L44             0 FILE TULSA2
L45             0 FILE USAN
L46             0 FILE WELDASEARCH
L47             0 FILE WSCA
L48             0 FILE ADISCTI
L49             0 FILE ADISINSIGHT
L50             0 FILE ADISNEWS
L51             0 FILE AQUASCI
L52             0 FILE BIOBUSINESS
L53             3 FILE BIOSIS
L54             0 FILE BIOTECHDS
L55             0 FILE CANCERLIT
L56             0 FILE CROPB
L57             0 FILE CROPU
L58             0 FILE DGENE
L59             0 FILE DRUGB
L60             0 FILE DRUGMONOG2
L61             0 FILE IMSDRUGNEWS
L62             0 FILE DRUGU
L63             0 FILE IMSRESEARCH
L64             0 FILE EMBAL
L65             9 FILE EMBASE
L66             5 FILE ESBIOBASE
L67             0 FILE FOMAD
L68             0 FILE FOREGE
L69             0 FILE FROSTI
L70             0 FILE FSTA
L71             0 FILE HEALSAFE
L72             0 FILE IFIPAT
L73             0 FILE IMSPRODUCT
L74             0 FILE LIFESCI
L75             0 FILE MEDICONF
L76             2 FILE MEDLINE
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L77           0 FILE NUTRACEUT
L78           0 FILE OCEAN
L79           0 FILE PCTGEN
L80           0 FILE PHAR
L81           0 FILE PHARMAML
L82           0 FILE PHIC
L83           0 FILE PHIN
L84           0 FILE SYNTHLINE
L85           0 FILE TOXCENTER
L86           3 FILE USPATFULL
L87           1 FILE USPAT2
L88           0 FILE VETB
L89           0 FILE VETU
L90           0 FILE WPIDS

TOTAL FOR ALL FILES
L91          42 OVULAT? (S) (OOCYTE (W) MATURAT?) (S) (PHOSPHODIESTERASE OR
                PDE? OR PDE4) AND CAMP

=> Dup rem l91
DUPLICATE IS NOT AVAILABLE IN 'AQUIRE, BIOCOMMERCE, CAOLD, FEDRIP, GENBANK,
INVESTEXT, KOSMET, RDISCLOSURE, STANDARDS, USAN, ADISINSIGHT, ADISNEWS, DGENE,
DRUGMONOG2, IMSRESEARCH, FOREGE, IMSPRODUCT, MEDICONF, NUTRACEUT, PCTGEN,
PHAR, PHARMAML, SYNTHLINE'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L91
L92           13 DUP REM L91 (29 DUPLICATES REMOVED)

=> d l92 1-12 ibib abs

L92  ANSWER 1 OF 13  USPATFULL on STN                    DUPLICATE 1
ACCESSION NUMBER:        2004:31803  USPATFULL
TITLE:                   CYCLIC AMP-SPECIFIC PHOSPHODIESTERASE INHIBITORS
INVENTOR(S):             Martins, Timothy J., Bothell, WA, UNITED STATES
                         Fowler, Kerry W., Seattle, WA, UNITED STATES
                         Odingo, Joshua, Everett, WA, UNITED STATES
                         Kesicki, Edward A., Bothell, WA, UNITED STATES
                         Oliver, Amy, Bothell, WA, UNITED STATES
                         Burgess, Laurence E., Boulder, CO, UNITED STATES
                         Gaudino, John J., Longmont, CO, UNITED STATES
                         Jones, Zachary S., Westminster, CO, UNITED STATES
                         Newhouse, Bradley J., Broomfield, CO, UNITED STATES
                         Schlachter, Stephen T., Boulder, CO, UNITED STATES
PATENT ASSIGNEE(S):      ICOS Corporation (U.S. corporation)

                              NUMBER         KIND    DATE
                         ---------------- ------ --------
PATENT INFORMATION:      US 2004023945      A1   20040205
                         US 6716871         B2   20040406
APPLICATION INFO.:       US 2002-151202     A1   20020517  (10)
RELATED APPLN. INFO.:    Division of Ser. No. US 2000-717956, filed on 21 Nov
                         2000, GRANTED, Pat. No. US 6423710 Continuation-in-part
                         of Ser. No. US 1999-471846, filed on 23 Dec 1999,
                         GRANTED, Pat. No. US 6258833
DOCUMENT TYPE:           Utility
FILE SEGMENT:            APPLICATION
LEGAL REPRESENTATIVE:    MARSHALL, GERSTEIN & BORUN LLP, 6300 SEARS TOWER, 233
                         S. WACKER DRIVE, CHICAGO, IL, 60606
NUMBER OF CLAIMS:        46
EXEMPLARY CLAIM:         1
LINE COUNT:              7955
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB       Novel pyrrolidine compounds that are potent and selective inhibitors of
         PDE4, as well as methods of making the same, are disclosed. Use of the
         compounds in the treatment of inflammatory diseases and other diseases
         involving elevated levels of cytokines, as well as central nervous
```

system (CNS) disorders, also is disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L92 ANSWER 2 OF 13 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:295561 BIOSIS
DOCUMENT NUMBER: PREV200300295561
TITLE: Cyclic nucleotide phosphodiesterase 3A is essential for mouse oocyte maturation.
AUTHOR(S): Masciarelli, Silvia [Reprint Author]; Liu, Chengyu; Park, Sun-Hee; Hockman, Steven; Jin, Catherine; Conti, Marco; Manganiello, Vincent
CORPORATE SOURCE: NHLBI, NIH, 9000 Rockville Pike, Bethesda, MD, 20892, USA masciars@nhlbi.nih.gov; liuch@nhlbi.nih.gov; parksh@nhlbi.nih.gov; hockmans@nhlbi.nih.gov; catherine.jin@stanford.edu; marco.conti@stanford.edu; manganiv@nhlbi.nih.gov
SOURCE: FASEB Journal, (March 2003) Vol. 17, No. 4-5, pp. Abstract No. 372.3. http://www.fasebj.org/. e-file.
Meeting Info.: FASEB Meeting on Experimental Biology: Translating the Genome. San Diego, CA, USA. April 11-15, 2003. FASEB.
ISSN: 0892-6638 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 25 Jun 2003
Last Updated on STN: 25 Jun 2003

AB Mammalian oocytes, physiologically arrested in prophase 1 due to elevated **cAMP**, resume meiosis following the pre-ovulatory gonadotropin LH surge. Pharmacological studies in mice and rats demonstrated that **PDE3** inhibitors block **oocyte maturation** in vivo and in vitro, without affecting **ovulation**, suggesting that **PDE3A** exerts a pivotal role in oocyte reentry into the cell cycle. To further investigate this role of PDE3A, PDE3A-null mice were generated by homologous recombination. PDE3A KO females exhibit normal mating behavior, but are completely sterile. Once removed from follicles, cultured oocytes undergo spontaneous maturation and resume meiosis, manifested by nuclear germinal vesicle break down (GVBD). Whereas WT oocytes mature within 3 hours, PDE3A KO oocytes did not undergo GBVD in vitro after 24 h. Although ovaries from the PDE3A KO mice display normal gross and microscopic structure and morphology, as well as spontaneous and hormone-stimulated ovulation (in terms of ovulated oocytes migrating through oviducts to the uterus), ovulated oocytes are arrested in meiotic prophase, as demonstrated by the persistence of GV, indicating that infertility in PDE3A null mice is due to oocyte inability to resume meiosis. Our in vivo model suggests that mouse oocyte PDE3A activity is required for physiological completion of oocyte maturation, and, consequently, fertilization. Research supported by NHLBI, NIH.

L92 ANSWER 3 OF 13 USPATFULL on STN
ACCESSION NUMBER: 2002:181688 USPATFULL
TITLE: Cyclic AMP-specific phosphodiesterase inhibitors
INVENTOR(S): Martins, Timothy J., Bothell, WA, United States
Fowler, Kerry W., Seattle, WA, United States
Odingo, Joshua, Everett, WA, United States
Kesicki, Edward A., Bothell, WA, United States
Oliver, Amy, Bothell, WA, United States
Burgess, Laurence E., Boulder, CO, United States
Gaudino, John J., Longmont, CO, United States
Jones, Zachary S., Westminster, CO, United States
Newhouse, Bradley J., Broomfield, CO, United States
Schlachter, Stephen T., Boulder, CO, United States
PATENT ASSIGNEE(S): ICOS Corporation, Bothell, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6423710	B1	20020723
APPLICATION INFO.:	US 2000-717956		20001121 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1999-471846, filed on 23 Dec 1999, now patented, Pat. No. US 6258833
DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Higel, Floyd D.
ASSISTANT EXAMINER: Sackey, Ebenezer
LEGAL REPRESENTATIVE: Marshall, Gerstein & Borun
NUMBER OF CLAIMS: 27
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 0 Drawing Figure(s); 0 Drawing Page(s)
LINE COUNT: 7458
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Novel pyrrolidine compounds that are potent and selective inhibitors of PDE4, as well as methods of making the same, are disclosed. Use of the compounds in the treatment of inflammatory diseases and other diseases involving elevated levels of cytokines, as well as central nervous system (CNS) disorders, also is disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L92 ANSWER 4 OF 13 BIOTECHNO COPYRIGHT 2004 Elsevier Science B.V. on STN DUPLICATE

ACCESSION NUMBER: 2002:34436944 BIOTECHNO
TITLE: Role of cyclic nucleotide signaling in oocyte maturation
AUTHOR: Conti M.; Andersen C.B.; Richard F.; Mehats C.; Chun S.Y.; Horner K.; Jin C.; Tsafriri A.
CORPORATE SOURCE: M. Conti, Division of Reproductive Biology, Department of Gynecology/Obstetrics, Stanford University School Medicine, Stanford, CA 94305, United States. E-mail: marco.conti@stanford.edu
SOURCE: Molecular and Cellular Endocrinology, (22 FEB 2002), 187/1-2 (153-159), 56 reference(s) CODEN: MCEND6 ISSN: 0303-7207
PUBLISHER ITEM IDENT.: S0303720701006864
DOCUMENT TYPE: Journal; Conference Article
COUNTRY: Ireland
LANGUAGE: English
SUMMARY LANGUAGE: English

AN 2002:34436944 BIOTECHNO
AB The development of the ovarian follicle, **oocyte maturation**, and **ovulation** require a complex set of endocrine, paracrine, and autocrine inputs that are translated into the regulation of cyclic nucleotide levels. Changes in intracellular **cAMP** mediate the gonadotropin regulation of granulosa and theca cell functions. Likewise, a decrease in **cAMP** concentration in the oocyte has been associated with the resumption of meiosis. Using pharmacological and molecular approaches, we determined that the expression of cyclic nucleotide **phosphodiesterases** (**PDEs**), the enzymes that degrade and inactivate **cAMP**, is compartmentalized in the ovarian follicle of all species studied, with **PDE3** present in the oocytes and **PDE4s** in granulosa cells. The **PDE3** expressed in the mouse oocyte was cloned, and the protein expressed in a heterologous system had properties similar to those of a **PDE3A** derived from somatic cells. Inhibition of the oocyte **PDE3** completely blocked **oocyte maturation** in vitro and in vivo, demonstrating that the activity of this enzyme is essential for **oocyte maturation**. Heterologous expression of **PDE3A** in Xenopus oocyte causes morphological changes distinctive of resumption of meiosis (GVBD), as well as activation of mos translation and MAPK phosphorylation. Using mRNA and antibody microinjection in the Xenopus eggs, we have shown that

PDE3 is downstream from the kinase PKB/Akt in the pathway that mediates IGF-1 but not progesterone-induced meiotic resumption. The presence of a similar regulatory module in mammalian oocytes is inferred by pharmacological studies with **PDE3** inhibitors and measurement of **PDE** activity. Thus, **PDE3** plays an essential role in the signaling pathway that controls resumption of meiosis in amphibians and mammals. Understanding the regulation of this enzyme may shed some light on the signals that trigger **oocyte maturation**. Copyright .COPYRGT. 2002 Elsevier Science Ireland Ltd.

L92 ANSWER 5 OF 13 USPATFULL on STN

ACCESSION NUMBER:	2000:113500 USPATFULL
TITLE:	Non-hormonal method of contraception
INVENTOR(S):	Conti, Marco, Stanford, CA, United States Hsueh, Aaron J. W., Stanford, CA, United States Tsafriri, Alexander, Rehovot, Israel
PATENT ASSIGNEE(S):	The Board of Trustees of the Leland Stanford Junior University, Stanford, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6110471		20000829	
APPLICATION INFO.:	US 1997-928805		19970912	(8)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1996-26090P	19960913 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Kishore, Gollamudi S.
ASSISTANT EXAMINER:	Channavajjala, Lakshmi
LEGAL REPRESENTATIVE:	Sholtz, Charles K., Stratford, Carol A., Mohr, Judy M.
NUMBER OF CLAIMS:	15
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	23 Drawing Figure(s); 8 Drawing Page(s)
LINE COUNT:	1089

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of contraception by delivering to the ovaries of a female mammal a pharmaceutically-effective dose of a PDE3-specific inhibitor at about the time of ovulation.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L92 ANSWER 6 OF 13 CABA COPYRIGHT 2004 CABI on STN DUPLICATE 3

ACCESSION NUMBER:	1998:160713 CABA
DOCUMENT NUMBER:	19980107482
TITLE:	**Phosphodiesterase** 3 inhibitors suppress **oocyte maturation** and consequent pregnancy without affecting **ovulation** and cyclicity in rodents
AUTHOR:	Wiersma, A.; Hirsch, B.; Tsafriri, A.; Hanssen, R. G. J. M.; Kant, M. van de; Kloosterboer, H. J.; Conti, M.; Hsueh, A. J. W.; Van de Kant, M.
CORPORATE SOURCE:	Department of Pharmacology, N.V. Organon, P.O. Box 20, 5340 BH Oss, Netherlands.
SOURCE:	Journal of Clinical Investigation, (1998) Vol. 102, No. 3, pp. 532-537. 37 ref. ISSN: 0021-9738
DOCUMENT TYPE:	Journal
LANGUAGE:	English
ENTRY DATE:	Entered STN: 19981111 Last Updated on STN: 19981111

AB Although gonadotropins stimulate **cAMP** production in somatic cells of the follicle, a decrease in intra-oocyte **cAMP** levels is

required for resumption of meiosis in oocytes. Inhibitors of the **cAMP**-degrading enzyme **phosphodiesterase** 3 were used to block meiosis in **ovulating** oocytes in rodents (B6D2-F1 and C57B1/2J mice and Sprague-Dawley and Orga rats). Fertilization and pregnancy were prevented without disturbing follicle rupture and normal oestrous cyclicity. In contrast to conventional contraceptive pills, which disrupt ovarian steroidogenesis and reproductive cycles, this method produced contraception by selective blockage of **oocyte maturation** and development without alterations in **ovulation** and reproductive cyclicity.

L92 ANSWER 7 OF 13 BIOTECHNO COPYRIGHT 2004 Elsevier Science B.V. on STN
DUPLICATE

ACCESSION NUMBER: 1998:29003189 BIOTECHNO
TITLE: Genetics of male infertility
AUTHOR: Hargreave T.B.; Ghosh C.; Cooke H.
CORPORATE SOURCE: T.B. Hargreave, Department of Urology, Fertility Problems Clinic, Western General Hospital, Edinburgh EH4 2XU, United Kingdom.
SOURCE: Molecular and Cellular Endocrinology, (25 OCT 1998), 145/1-2 (143-151), 67 reference(s)
CODEN: MCEND6 ISSN: 0303-7207
PUBLISHER ITEM IDENT.: S0303720798001816
DOCUMENT TYPE: Journal; Conference Article
COUNTRY: Ireland
LANGUAGE: English
SUMMARY LANGUAGE: English

AN 1998:29003189 BIOTECHNO

AB In the follicles of the mammalian and amphibian ovary, **oocyte maturation** is arrested at the prophase of the first meiotic division. Prior to **ovulation**, oocytes re-enter the cell cycle, complete the meiotic division and extrude the first polar body. Work from several laboratories including ours has provided evidence that the **cAMP**-mediated signal transduction pathways play an important role in the regulation of meiosis, the cyclic nucleotide acting as a negative regulator of maturation. Since **cAMP** can be regulated both at the level of synthesis and degradation, our laboratory is investigating the role of **phosphodiesterases** (**PDE**) in the control of **cAMP** levels of oocytes. Using pharmacological and molecular tools, we have determined that a **PDE3** is the enzyme involved in the control of **cAMP** levels in the oocytes. In vitro and in vivo studies have established that inhibition of the oocyte **PDE3** blocks resumption of meiosis. Furthermore, we have provided evidence that activation of a **PDE** is per se sufficient to cause resumption of meiosis in an amphibian oocyte model. The pathways regulating this **PDE** isoform expressed in the oocyte is under investigation, as they may uncover the physiological signals controlling meiosis.

L92 ANSWER 8 OF 13 BIOTECHNO COPYRIGHT 2004 Elsevier Science B.V. on STN
DUPLICATE

ACCESSION NUMBER: 1998:29003171 BIOTECHNO
TITLE: Role of cyclic nucleotide phosphodiesterases in resumption of meiosis
AUTHOR: Conti M.; Andersen C.B.; Richard F.J.; Shitsukawa K.; Tsafriri A.
CORPORATE SOURCE: M. Conti, Division of Reproductive Biology, Dept. of Gynecology and Obstetrics, Stanford Univ. School of Medicine, Stanford, CA 94305-5317, United States.
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SOURCE: Molecular and Cellular Endocrinology, (25 OCT 1998), 145/1-2 (9-14), 36 reference(s)
CODEN: MCEND6 ISSN: 0303-7207
PUBLISHER ITEM IDENT.: S0303720798001877
DOCUMENT TYPE: Journal; Conference Article
COUNTRY: Ireland
LANGUAGE: English

SUMMARY LANGUAGE: English
AN 1998:29003171 BIOTECHNO
AB In the follicles of the mammalian and amphibian ovary, **oocyte maturation** is arrested at the prophase of the first meiotic division. Prior to **ovulation**, oocytes reenter the cell cycle, complete the meiotic division, and extrude the first polar body. Work from several laboratories including ours has provided evidence that the **cAMP**-mediated signal transduction pathway plays an important role in regulation of meiosis, the cyclic nucleotide acting as a negative regulator of maturation. Since **cAMP** can be regulated both at the level of synthesis and degradation, our laboratory is investigating the role of **phosphodiesterases** (**PDE**) in the control of **cAMP** levels of oocytes. Using pharmacological and molecular tools, we have determined that a **PDE3** is the enzyme involved in the control of **cAMP** levels in the oocytes. In vitro and in vivo studies have established that inhibition of the oocyte **PDE3** blocks resumption of a **PDE** is per se sufficient to cause resumption of meiosis in an amphibian oocyte model. The pathways regulating this **PDE** isoform expressed in the oocyte is under investigation, as they may uncover the physiological signals controlling meiosis.

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DUPLICATE
ACCESSION NUMBER: 1996:26365046 BIOTECHNO
TITLE: Oocyte maturation involves campartmentalization and opposing changes of **cAMP** levels in follicular somatic and germ cells: Studies using selective phosphodiesterase inhibitors
AUTHOR: Tsafriri A.; Chun S.-Y.; Zhang R.; Hsueh A.J.W.; Conti M.
CORPORATE SOURCE: Department of Biological Regulation, Bernhard Zondek Hormone Res. Lab., Weizmann Institute of Science,Rehovot 76100, Israel.
SOURCE: Developmental Biology, (1996), 178/2 (393-402)
CODEN: DEBIAO ISSN: 0012-1606
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1996:26365046 BIOTECHNO
AB The second messenger **cAMP** has been implicated in the regulation of mammalian and amphibian **oocyte maturation**. Although a decrease in intraoocyte levels of **cAMP** precedes germinal vesicle breakdown (GVBD), the gonadotropin induction of **ovulation** and **oocyte maturation** is associated with major increases of **cAMP** in ovarian follicles. In the mammalian system, isolated oocytes undergo spontaneous maturation in vitro but this process is blocked by treatment with a **phosphodiesterase** (**PDE**) inhibitor, IBMX, which increases intraoocyte **cAMP** levels. In contrast, the same inhibitor, when added to cultured follicles for a brief time, increases follicle **cAMP** levels, followed by the induction of GVBD. To resolve the paradoxical actions of this **PDE** inhibitor on the maturation of isolated and follicle-endosed oocytes, we hypothesized that meiotic maturation requires opposing fluctuations of **cAMP** levels in the somatic granulosa and germ cells. Such apposing fluctuations may result from selective expression and regulation of **PDEs** in the somatic and germ cell compartments of the follicle. To test this hypothesis, **PDE** activity was manipulated in different follicular cells using type-specific inhibitors. The impact of the ensuing changes in **cAMP** levels in the two compartments was monitored by the induction of GVBD. In isolated oocytes, spontaneous GVBD was blocked by two inhibitors of type 3 **PDE** (cGMP-inhibited: CGI-**PDE**) milrinone and cilostamide. In contrast, treatment with an inhibitor for type 4 **PDE** (**cAMP**-specific),

rolipram, was ineffective. These findings suggest that the oocyte expresses type 3 but not type 4 **PDE** and that increases in intraoocyte **cAMP** suppress GVBD. This hypothesis was confirmed by in situ hybridization studies with **PDE3** and **PDE4** probes. **PDE3B** mRNA was concentrated in oocytes while **PDE4D** was mainly expressed in granulosa cells. In cultured follicles, LH treatment induced **oocyte maturation** but the gonadotropin action was blocked by inhibitors of type 3 but not the type 4 **PDE** inhibitors. Furthermore, treatment with the type 4, but not the type 3, **PDE** inhibitor mimics the action of LH and induces **oocyte maturation**, presumably by increasing **cAMP** levels in granulosa cells. Our findings indicate that **PDE** subtypes 4 and 3 are located in follicle somatic and germ cells, respectively. Preferential inhibition of **PDE** 3 in the oocyte may lead to a delay in **oocyte maturation** without affecting the **cAMP**-induced **ovulatory** process in the somatic cells. Conversely, selective suppression of granulosa cell **cAMP**-**PDE** may enhance the gonadotropin induction of **ovulation** and **oocyte maturation**. Thus, in addition to the well-recognized differential expression and regulation of adenylate cyclase in the somatic and germ cell compartments of the follicle, we suggest that selective regulation and expression of **PDEs** may be involved in the regulation of eAMP levels and control of **oocyte maturation** in the preovulatory mammalian follicle.

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DUPLICATE

ACCESSION NUMBER: 1990:20381769 BIOTECHNO
TITLE: Basic fibroblast growth factor induction of granulosa cell tissue-type plasminogen activator expression and oocyte maturation: Potential role as a paracrine ovarian hormone
AUTHOR: LaPolt P.S.; Yamoto M.; Veljkovic M.; Sincich C.; Ny T.; Tsafriri A.; Hsueh A.J.W.
CORPORATE SOURCE: Dept. Reproductive Medicine, Univ. California, San Diego,La Jolla, CA 92093, United States.
SOURCE: Endocrinology, (1990), 127/5 (2357-2363)
CODEN: ENDOAO ISSN: 0013-7227
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English

AN 1990:20381769 BIOTECHNO

AB Gonadotropin-induced **ovulation** is associated with **oocyte maturation** and preovulatory increases of tissue plasminogen activator (tPA) expression. Basic fibroblast growth factor (bFGF), an angiogenic factor found in many organs including the ovary, modulates steroidogenesis in granulosa cells and increases PA activity in endothelial cells. Here studies were performed to examine the possible roles of bFGF as an intragonadal regulator of tPA expression and **oocyte maturation**. In cultured granulosa cells, bFGF caused a time-dependent (onset at 24 h) and dose-dependent (ED.sub.5.sub.0 = 0.6 nM) increase (up to 5-fold) in tPA enzyme activity as measured by the fibrin overlay technique. Northern blot hybridization also revealed that treatment of cells with bFGF (2 nM) increased the level of the 22S tPA messenger RNA. Slot blot analysis indicated that the effects of bFGF were time dependent and dose dependent; tPA message levels increase before tPA activity levels. bFGF (0.6 nM) also significantly increased granulosa cell **cAMP** production in both the absence and presence of a **phosphodiesterase** inhibitor. In follicle-enclosed oocytes incubated for 24 h in media with or without increasing concentrations of LH or bFGF, germinal vesicle breakdown was observed in only 1.6% of controls, but 85% of LH (1 μg/ml)-treated oocytes underwent maturation. Likewise, bFGF induced germinal vesicle breakdown (10-80%) over a dose range of 0.6 to 333 nM. In the same

follicles, bFGF, like LH, also stimulated prostaglandin E production. These results, coupled with the identification of bFGF in growing follicles, suggest that bFGF acts as an intraovarian inducer of granulosa cell tPA gene expression and **oocyte maturation**.

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DUPLICATE
ACCESSION NUMBER: 1983:13130538 BIOTECHNO
TITLE: A comparative study of the mechanism of action of luteinizing hormone and a gonadotropin releasing hormone analog on the ovary
AUTHOR: Dekel N.; Sherizly I.; Tsafriri A.; Naor Z.
CORPORATE SOURCE: Dep. Horm. Res., Weizmann Inst. Sci., Rehovot 76100, Israel.
SOURCE: Biology of Reproduction, (1983), 28/1 (161-166)
CODEN: BIREBV
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
AN 1983:13130538 BIOTECHNO
AB The mechanism of action of a gonadotropin releasing hormone (GnRH) agonistic analog (¢D-Ala.sup.6!GnRH) on the rat ovary has been studied in comparison to similar effects of luteinizing hormone (LH). Stimulation of meiosis resumption in vitro in follicle-enclosed oocytes by both LH and ¢D-Ala.sup.6!GnRH, was blocked by elevated levels of **cAMP** as demonstrated when either dibutyryl **cAMP** or the **phosphodiesterase** inhibitor methylisobutylxanthine was present in the culture medium. In vivo, the prostaglandin synthase inhibitor indomethacin, which blocks LH-induced **ovulation**, also inhibited **ovulation** induced by the GnRH analog in hypophysectomized rats. On the other hand, the potent GnRH-antagonist ¢D-pGlu.sup.1, pClPhe.sup.2, D-Trp.sup.3.sup.,.sup.6!GnRH which blocked the stimulatory effect of the agonist on **oocyte maturation** and **ovulation** had no effect on LH action. It is concluded that while a GnRH-like peptide does not seem to mediate LH action on the ovarian follicles, both LH and GnRH agonist share some common mechanistic pathways at a post-receptor locus.

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DUPLICATE
ACCESSION NUMBER: 1981:12226812 BIOTECHNO
TITLE: Modulation of cell-to-cell communication in the cumulus-oocyte complex and the regulation of oocyte maturation by LH
AUTHOR: Dekel N.; Lawrence T.S.; Gilula N.B.; Beers W.H.
CORPORATE SOURCE: Dept. Biol., New York Univ., New York, NY 10003, United States.
SOURCE: Developmental Biology, (1981), 86/2 (356-372)
CODEN: DEBIAO
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
AN 1981:12226812 BIOTECHNO
AB Prior to **ovulation**, cell-to-cell communication between the oocyte and the cells of the cumulus oophorus is terminated. In this paper we report that LH, Bt.sub.2-**cAMP**, and the cyclic nucleotide **phosphodiesterase** inhibitor, 3-isobutyl-1-methylxanthine, are all capable of interrupting communication in vitro in rat follicle-enclosed cumulus oocyte complexes. Moreover, the breakdown of communication appears to be closely correlated with the ability of hyaluronidase to disperse the cumulus cell mass. This observation allows simple screening of the effects of various agents on cumulus-oocyte communication. The in vitro system employed in this study has also been used to investigate the relationship between communication and **oocyte maturation**. The findings presented indicate that the interrutpion of communication between the cumulus and the oocyte leads to relief of

meiotic arrest, and are consistent with the possibility tht **cAMP** , transmitted from the cumulus to the oocyte, may be the inhibitor of **oocyte maturation** in vivo.

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